Biopharmaceutical aspects and implications of excipient variability in drug product performance

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Abstract

Implementation of Quality by Design approaches in pharmaceutical industry requires a sound understanding of the parameters triggering final product variability. Excipients, although generally regarded as inert components, are of great significance in terms of solid dosage form development and any variation in the material attributes may impact drug product performance. Sourcing, production and processing are contributing factors to excipient variability. Interchange between different suppliers can lead to final products with different quality attributes. Identification of excipient critical material attributes is not straightforward, as criticality must be linked to functionality and it is well recognized that the mechanisms by which excipients exert their action are not fully understood. Investigating the impact of excipient variability on *in vitro* dissolution could enable scientists to get an insight on the *in vivo* behavior of drug products and potentially tolerate variability. A thorough understanding of excipient material properties, product components interactions and the effect of the gastrointestinal tract heterogeneity on excipients and drug release is recommended. This review aims to present current knowledge on excipient critical material attributes and their link to biopharmaceutical behavior and dissolution characteristics. Attempts to describe the impact of physiological conditions on excipient functionality are also addressed. Excipient properties that are considered crucial to drug product performance in a biorelevant perspective are elucidated.

Keywords: Excipients; Dissolution; Solid Dosage Form; Solubility; Gastrointestinal; Polymers; Variability.

1. Introduction

Pharmaceutical development is now entering the new era of quality build. The traditional three batch validation is currently fading as batch failures, product recalls, drug shortages are still present in the pharmaceutical market. Regulatory agencies tend to impose more strict product specifications for new drug applications (NDAs), abbreviated new drug applications (ANDAs), biowaiver extensions and require a profound understanding of active pharmaceutical ingredient (API), excipient and product manufacturing, as well as, any interaction between these parameters that may affect final product safety and efficacy. In an attempt of amelioration, pharmaceutical industry is implementing the principles of Quality by Design (QbD). The aim is to build robust manufacturing processes in order to assure that the desirable product is constantly delivered to the patient through the establishment of a design space that defines the permissible area where variability and/or variations of input materials will not affect the outcome of the production process. Reducing or tolerating final product variation requires a profound understanding of all factors playing a crucial role in finished dosage forms. Controlling these crucial parameters will allow the design of products that will consistently meet final requirements, contribute to minimization of regulatory constraints and enable the safe passage from batch to continuous manufacturing, a beneficial production technique to address industrial deficiencies [1]. Excipients constitute a major component of final products and it is recognized that variability in their material properties can impact product processing, manufacturing and performance [2, 3]. The exact mechanisms by which excipients exert their action are still to be discovered, especially when drug product performance is concerned [4, 5]. The gastrointestinal heterogeneity and its effect on excipient functionality is an additional challenge in understanding and controlling the role of excipients in drug release.

A comprehensive overview of the current knowledge on excipient variability and its effect on solid dosage form performance is presented in this review. The biopharmaceutical parameters that impact the functional role of key excipients used in solid formulations is discussed. The aim is to gain a basic understanding of potential critical material attributes and their link to excipient and final drug product variability.

2. Excipient variability in drug development

As mentioned in the ICH Q8 “the aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product” [6]. A final dosage form should meet a number of specifications to justify its efficacy and safe use. Deviation from these acceptance criteria indicates variability of final dosage forms. Variation is difficult to control since random distribution prevails in everything [7]. QbD aims towards controlling variability by i. defining the final product attributes that will justify the intended use of final products and ii. deliberately designing the production process and establishing the design space and control strategy to always meet these final attributes. Aspects whose variability can compromise product quality are characterized by high criticality. Critical quality attributes refer to aspects of the output product while critical material attributes to input materials [8]. In terms of pharmaceutical development, factors that may trigger final product variability include: active pharmaceutical ingredients (APIs), excipients and process parameters [8]. The physicochemical properties of the two former, any deviations or alterations in the latter and the complex interplay of process parameters and material attributes contribute to the incline in quality specifications. It becomes clear that in order to control the outcome we must have a fundamental

68 understanding and control of all input materials. The required understanding of the reasons triggering product variability and batch
69 failures is needed towards continuous pharmaceutical production and may not always be an easy task [9].

70 The impact of manufacturing processes on drug product quality has been addressed [10-12] but a more comprehensive
71 approach towards drug product components is yet to be made. Examining the effect of input materials (e.g. APIs and excipients) on
72 finished solid dosage forms requires a linkage of material properties to product quality attributes [13]. A thorough understanding of
73 molecular, structural and particle properties of a substance is necessary. The limited knowledge on the role of physical and chemical
74 properties of pharmaceutical components hinders the possibility to further optimize the behavior of oral solid dosage forms throughout
75 manufacturing, but this gap is more pronounced in drug product performance. A change in a critical attribute for dissolution will not
76 only cause production or regulatory failures, but it may strongly affect drug bioavailability. The complexity of the gastrointestinal
77 environment adds a further challenge in investigating the effect of material attributes variability in drug dissolution. Although the API
78 is considered the most substantial product component for disease treatment, it has to be noted that excipients can be more important in
79 processes prior to oral drug absorption and also can induce even treatment failure if the drug is not appropriately released and
80 dissolved according to product specifications. From manufacturing through to *in vivo* functional performance, excipients exert their
81 action but their properties can affect drug dissolution, as it will be revealed by the critical analysis performed in this review. Since
82 excipients constitute a large portion of a solid dosage form, comprising up to 99% of the total formulation mass [14], their impact on
83 quality attributes can be statistically significant. The broad range of the excipient level used in solid dosage forms along with a
84 possible alteration in excipient functionality by level variation, complicates further the excipient variability issue. *In vitro* and/ or *in*

vivo excipient effects on drug solubility, dissolution and permeability could impact oral bioavailability and bioequivalence. The use of a different type of excipient with the same intended functionality could also be problematic as the diversity of material properties may result in a change of the overall product performance. Understanding and integrating excipient variability in the production's design space and control strategy will pave the way for building robust production processes both in batch and continuous manufacturing [15].

3. Sources of excipient variability

Final product variability either preexists or is created during manufacturing. In this review, we are focusing on inherent excipient variability and its effect on final drug product. The main reasons for excipient variability are: i. raw material sourcing which includes environmental variations that may lead to different raw material properties and ii. manufacturing which refers to excipient variability caused by a change during excipient production and can be divided into inter and intra-supplier.

Natural sourcing: The majority of excipients are naturally derived products or semi-synthetic compounds (produced after chemical modification of a natural product). They are bound, therefore, with inevitable variability caused by environmental alterations (natural, regional, seasonal) [16]. Sourcing of raw materials is a major factor for excipient variability. For example, microcrystalline cellulose can be produced by wood (softwood/hardwood) or cotton. A first study on four brands of microcrystalline cellulose (two brands derived from softwood and two from hardwood) examining lignin and hemicellulose content determined excipient origins. Significant variations in chemical structure, crystal structure and particle size were observed [17]. Differences in lignin content may be

the cause for the increased dissolution rate of prednisone tablets manufactured with microcrystalline cellulose from different sources [18]. Controlling the source of excipients can reduce variation but still any unavoidable natural complications may lead to production of different raw materials.

Manufacturing: Excipients are manufactured by chemical companies for use in pharmaceutical, chemical, and food industry. A common strategy for pharmaceutical companies is to have more than one supplier in order to constantly meet market demands [14]. Changes in excipient supplier has been shown to contribute to excipient variability. Supplier to supplier variability may arise either from different natural sourcing or different manufacturing processes. For instance, significant intersupplier variability was observed in anhydrous lactose solid state properties (specific surface area, tensile strength, yield pressure) that could impact final dosage forms according to the amount of excipient used and the interplay with the other dosage form components [19]. Other examples of intersupplier variability are reporting differences in intrinsic viscosity, mean molecular weight, mean particle size and water uptake rate between two interchangeable Hydroxypropyl cellulose (HPC) brands [20], and in particle size and surface area between different magnesium stearate suppliers [21] . Although, intersupplier variability may seem more reasonable, intrasupplier variability referring to batch-to-batch or lot-to-lot variation in excipient production has been reported as well. A notable example of interlot excipient variability and its effect on final dosage form refers to a study by Perez et al. on lot to lot variability of Carbomer 943. The two dissimilar lots were found to greatly affect *in vitro* release rates of hydrochlorothiazide (HCTZ) matrix tablets, due to differences in mean molecular weight of carbomer [22]. Even a slight change in manufacturing procedures or parameters may have an effect on the product functionality. For example, two batches of soluble starch differing only in one additional washing step with acetone were

studied. Although, in terms of routine characterization the two batches were found identical, their compaction properties showed large variation due to their differences in the surface area caused by the extra washing step [23].

Inadequate specifications: Pharmacopeial specifications clearly address excipient identification but functionality specifications are not straightforward since excipient function is formulation/application dependent [3]. For instance, when hypromellose is used as a binder, viscosity and degree of substitution are considered functional properties, but additional properties (particle size distribution, powder flow) need to be controlled when the excipient is used as a release modifier [24]. Excipient demand is increased in the Food/Chemical/Cosmetic Industry,, and the quality tests prescribed to suppliers assuring excipient quality (identity, quality, purity) [3] focus mainly on their needs. This minimum of regulatory specifications may suffice for these industries, but pharmaceutical companies have to deal more strictly with excipient variability and be assured that the properties rendering excipients functional are "present" in every batch within appropriate limits. A first issue that arises from current monograph specifications is that they cannot adequately set the appropriate limits in functional specifications ("one-point" limits [25] or a wide range of acceptance values). Without prior mechanistic knowledge of the actual excipient role, variability could be detrimental, even if excipient property values meet monograph specifications [25]. The need for functional evaluation is encouraged with the introduction of Excipient Functionality Related Characteristics (FRCs) by the European Pharmacopeia and the General Information Chapter on "Excipient Performance <1059>" by the United States Pharmacopeia. Still, the terminology of excipient functionality is not straight-forward. The underlying mechanisms of excipient use in several cases are not known and further investigations are necessary in order to establish functionality tests, as excipient role should be addressed in case-by-case, function-by-function and product component interactive

perspective. The proposed FRC tests are not mandatory and mostly address chemical identification rather linking physical and chemical properties to excipient function [3]. Drug product manufacturers should gain a more thorough knowledge on excipient production and characteristics to get an insight when changing excipient suppliers in order to assure that excipient functionality and material properties remain consistent.

4. Biopharmaceutical aspects of excipients

Formulation scientists recognize the importance of excipient variability in drug product design. Reports in literature though address mainly drug product processing/manufacturability [26] and not drug product performance in terms of drug release from a solid dosage form and drug bioavailability. An interplay between *in vitro* conditions (i.e. dissolution medium composition, temperature, agitation) and *in vivo* physiological factors (i.e. gastrointestinal factors) and excipient functionality can impact drug bioavailability (Figure 1). Excipient presence in the luminal fluids triggers modifications in the gastrointestinal environment and gastrointestinal conditions may alter excipient material attributes leading to different functionality, with an effect in drug absorption in both cases. This strong interplay will complicate even more final product variability and bioequivalence, if not thorough investigated.

4.1 Effect of excipients on physiological conditions

Traditionally the effect of excipients, on drug product performance was considered of minor importance, due to their pharmacological inactivity. Only after the beginning of 90s, and with the foundation of the International Pharmaceutical Excipient Council (IPEC), investigation of their significance on finished drug products started [27]. An increased number of case studies

indicate that excipients may influence bioavailability and impede the establishment of bioequivalence between products. Novel formulations addressing the poor aqueous solubility of drugs, contain excipients that affect drug solubility, permeability (passive or active) and metabolism [28]. Solubilizers enhance the solubility of poorly soluble drugs and may decrease drug permeation through the intestinal epithelium due to the lower free drug fraction available for absorption [29]. A number of excipient classes have been demonstrated to affect tight junctions integrity [30], active transporters, [31, 32] and cytochrome P450 activity [33, 34]. Excipient effects on other physiological factors, e.g. gastric residence time, small intestinal transit time, mucus integrity, physiological pH and motility, have been extensively reviewed [35]. These interactions present a challenge on current considerations about the role of excipients on product performance and regulatory guidelines require extensive proofs of excipient inertness in each product [36, 37]. Biowaivers have been correlated to the Biopharmaceutical Classification System (BCS), and qualitatively and quantitatively similar excipients are required for biowaivers for immediate release formulations of BCS Class III compounds [37, 38]. According to WHO guidelines, an excipient can be used in multisource (generic) products requesting biowaiver even if it is not present in the comparator product, as long as it is present to other products containing the same API and have marketing authorization in countries participating in the International Committee of Harmonization [39]. Even in cases where excipients were not implied to affect bioequivalence, human bioavailability was altered with a change in the amount of an excipient or the addition of a new excipient in the generic product [40]. The addition of Sodium Lauryl Sulfate in a generic alendronate immediate release tablet (absent in the innovator alendronate (BCS III) tablet but present in generic alendronate tablets approved in USA) led to a 5-6 fold increase of alendronate's bioavailability resulting in bioinequivalence [40]. Drug permeability can be affected or not by the presence of excipients as revealed by in vitro

permeability studies (Caco-2 models). The presence of lactose, HPMC and PEG did not alter the permeability of BCS Class III compounds [41]. A drug dependent excipient effect has been shown in the case of Tween 80 due to its P- glycoprotein (P-gp) inhibitory effect, as it increases the apparent permeability (P_{app}) of drugs that are P-gp substrates (e.g. cimetidine) while other drugs remain unaffected (e.g. atenolol, acyclovir) [42]. Sodium Lauryl Sulfate (SLS) shows a concentration-dependent effect on the permeation of low permeability drugs with an increase in the P_{app} when present in low concentrations (0.139 mM) [42] while at increased concentrations drug permeation is even greater due to excipient-mediated disruption of the cell monolayer [41, 42]. The *in vivo* impact of excipients on drug permeability has to be further investigated, as *in vitro* permeation models (such as Caco-2 monolayers) are more sensitive in excipient effects and may overestimate their impact [41]. Generalized conclusions should be avoided without prior scientific knowledge on the biopharmaceutical aspects of excipients. Although, there is a tendency to investigate the effect of excipients with a prominent role on dissolution and bioavailability (surfactants, carriers, bioadhesives, polymers, copolymers etc.), the intended product performance can be compromised even from excipients whose initial role is not related to drug release/dissolution [40].

4.2 Effect of physiological conditions on excipients

When formulating a solid dosage form, the varying composition and heterogeneity of the gastrointestinal tract need to be considered. Factors such as properties of the gastrointestinal contents (i.e. pH, ionic strength, temperature, viscosity, bile salts concentration) and gastrointestinal motility will have an impact on drug release. Gastric emptying will influence drug, excipient and

product characteristics. Moving from the acidic stomach to the more basic small intestine affects the ionization and solubility of weak acidic/basic drugs and subsequently their absorption. Moreover, the changes in physiological conditions by the presence of meal (fed state) can alter solid dosage form performance. Excipient properties and their functionality will be impacted by this heterogeneous environment (data indicating the effect of physiological conditions on excipient functionality is discussed in detail in the next sections of this review). Excipient variability should be addressed in a biorelevant perspective reflected in *in vitro* dissolution testing. The use of biorelevant media mimicking physiological gastrointestinal aspects in fasted and fed state (i.e. bile secretion, meal components, surface tension, osmolality) [43, 44] could enable the investigation of the gastrointestinal effect on excipient functionality and drug release. A better understanding of the complex excipient effects taking place in the gastrointestinal tract and their impact in product performance could be achieved by the combination of biorelevant *in vitro* dissolution testing with imaging techniques, where applicable [45].

5. Excipients in solid dosage forms

Particle size distribution, pore size distribution and surface area are critical properties for dissolution of solid dosage forms [13], but not the sole ones. In the following sections material properties of commonly used excipients in solid dosage forms are discussed, revealing their functional role on drug product performance. Excipients are categorized according to their function in solid dosage forms (Table 1) and cases related to their functionality or variability are reviewed.

5.1 Diluents

Diluents, referred also as fillers, are incorporated into solid dosage forms to adjust their mass. When low drug doses are required, fillers may comprise up to 90% of the total dosage weight to ensure adequate product processability throughout manufacturing. Despite the simplicity of their role, their high concentrations may render them high risk factors for product performance. Their physical and chemical properties are significant attributes for their functionality and may trigger dosage variability, but their impact is usually related to other product components. Diluents can be either inorganic or organic materials. Typically used diluents include: lactose, mannitol, microcrystalline cellulose and dicalcium phosphate [46].

5.1.1 Lactose

Lactose is a disaccharide consisted of D-galactose and D-glucose units linked through a β (1-4) glycosidic bond and is produced from bovine milk. Lactose is mainly used as soluble diluent in formulations, but it possesses binding properties as well[47].

Molecular Properties

Two anomeric forms of lactose, referred as α and β, are present, according to glucose stereochemistry. An interchange between the two isomers, called mutarotation, is observed in aqueous solution. When in equilibrium (0-100°C), the ratio between the two forms is approximately 60:40 for β and α lactose, respectively. They differ in physical properties such as melting point, density, specific optical rotation, and on solubility with β lactose being more soluble in water (20°C; 0.5 g/mL) than the α anomer (0.075 g/mL) [48]. The α isomer, according to temperature, may exist as monohydrate (<120°C) or anhydrous (>120°C) form, while β lactose is anhydrous [48].

These molecular differences affect lactose's solid state properties and products with varying attributes are available on the market. Presence of impurities in lactose brands may catalyze drug hydrolysis, affecting drug stability [49].

Structural Properties

Varying crystallization patterns are observed due to the presence of the two anomers and their solubility difference. The α isomer crystallizes as a monohydrate in low temperatures (<93 °C) in a variety of shapes (prism, pyramidal, tomahawk)[47]. Uneven-diamond shape crystals of 80% β-lactose anhydrous with a small portion of α-lactose anhydrous are formed with increased temperature (>93 °C) [48]. Spray-dried lactose, consisted of α-lactose monohydrate and amorphous lactose, in a spherical shape with excellent flow properties has also been produced. The structural differences lead to products with varying compactions forces [19]. Higher initial solubility and dissolution rate for the β-form was observed from different crystalline lactose powders in water at 37 °C, followed by a decrease in the order β-lactose (0.5 g/mL water) >α-lactose anhydrous (0.27 g/mL water) >α-lactose monohydrate (0.13 g/mL water) but due to mutarotation, final solubility for all lactose types was the same [47, 50]. Monohydrate α and β lactose disintegrated faster compared to anhydrous lactose and an increase in compression force resulted in increased disintegration time. The fast disintegration was attributed to the increased porosity of lactose tablets which allowed quick water penetration [50].

Particle Properties

Particle size distribution of lactose is not specified in pharmacopeias. Lactose brands with varying size distribution are available in the market[47] . When the effect of lactose particle size in product manufacturing was studied, it was shown that in direct

compression, an increase in lactose particle size will enhance blend flowability and form weaker tablets [51], due to decreased cohesiveness of particles. Studies on wet granulation behaviour of lactose linked particle size and size distribution to granule porosity. Small particle sizes (53 μm) give granules with higher porosity, as a result of the higher resistance of small particles to densification [52]. Narrow ranges of particle size (40-75 μm, 212-250 μm) produced granules of higher porosity due to the absence of fine particles that tend to occupy void volumes between larger particles [52]. As porosity is considered an important parameter for water penetration, particle properties of lactose can have a major impact on dissolution.

Level

Lactose may greatly enhance dissolution of poorly soluble drugs as the soluble diluent improves powder and tablet wettability. Studies on ethinamate capsules showed a decrease in drug release when 10% w/w lactose was used in the formulation but improved dissolution when diluent concentrations reached levels of 50% w/w [53]. Increasing the percentage of fine lactose in indomethacin formulations (interactive mixture of API and coarse lactose) resulted in improvement of the drug's dissolution rate, as rapid dissolution of lactose leaving open structures enables deagglomeration of indomethacin particles [54]. For a soluble drug (chloramphenicol) inclusion of lactose at 50% w/w in the capsule formulation had no effect on drug's dissolution. Increasing lactose to a level of 80% w/w slowed down chloramphenicol dissolution, as the dissolved diluent retards drug release [55]. The interplay between lactose content and drug's BCS class was recently portrayed in a top-down approach comparing marketed innovator and generic products with proved bioequivalence. For BCS class I and class III drugs relatively large differences in lactose level were

observed whereas for BCS class II and class IV drugs small variations in these levels were noted. The probability of bioinequivalence based on these differences in lactose levels between the innovator and generic products was classified as low or BCS class I drugs, medium for BCS class II and III drugs and high for BCS class IV drugs [56].

Biopharmaceutical Properties

Lactose can affect bioavailability through a dissolution modification effect. No impact on other physiological factors has been reported [56]. Interactions between milk proteins and lactose have been described. Low lactose concentrations decreased the viscosity of the milk dispersion (lactose assembles around protein molecules) whereas high lactose concentrations increased the viscosity of the dispersion (reduction in water-protein interactions) [57]. The potential interplay of meal intake and lactose on physiological factors and drug release and dissolution has not yet been investigated in a biopharmaceutical perspective.

5.1.2 Dicalcium Phosphate

Calcium phosphate dibasic, or dicalcium phosphate (DP), is an inorganic insoluble diluent used in tablet and capsule manufacturing.

Molecular and Structural Properties

Two hydration forms of dicalcium phosphate, anhydrous (DPA) and dihydrate (DPD), are used in pharmaceutical development[58, 59]. The anhydrous form occurs as a triclinic crystal while the dihydrate forms a monoclinic structure[58, 59]. Dicalcium phosphate dihydrate presents good flow properties and low hygroscopicity. According to temperature (40-50 °C) and humidity (32-75% relative

humidity) [60], though, it tends to lose water of hydration that may cause chemical instability of APIs in dosage forms [61]. The anhydrous form presents an alternative without compromising drug stability. The two forms differ in porosity, as a result of their different hydration. The anhydrous form exhibits higher porosity due to the absence of water in the crystal structure, leading to its better compressibility and faster disintegration [62].

Level

As for lactose, the effect of dicalcium phosphate on drug release is profound in high levels of the diluent. Replacing lactose with dicalcium phosphate dihydrate or anhydrous resulted in decreased and extended release of alprazolam from matrix tablets containing HPMC as well. In binary systems containing different ratios of lactose and dicalcium phosphate dihydrate, increasing the amount of the insoluble diluent did not impact dissolution rate, and only when, dicalcium phosphate dihydrate was the sole diluent and in high level (36.5% w/w) drug dissolution was affected [63].

Biopharmaceutical Properties

The pH difference of the stomach and intestinal contents is expected to affect dicalcium phosphate's behavior[64], due to its higher solubility in acidic media. In a comparative study on the effect of pH on superdisintegrant functionality (discussed in sections 5.4.1, 5.4.2, 5.4.3), the influence of different types of diluents on drug dissolution was evaluated. Swelling capacity of some disintegrants is lower in acidic medium, leading to reduced disintegration and dissolution. When lactose was the diluent, the reduced swelling of superdisintegrants caused a decrease in the dissolution of hydrochlorothiazide (HCTZ) tablets in acidic medium (0.1 N

278 HCl, pH=1; paddle method, 50 rpm, 37 °C). Substituting lactose to DPD led to higher drug release in the acidic solution, compared to
279 water and the effect of superdisintegrant swelling to reduce dissolution in acidic media was not observed (Figure 2) [65]. Although the
280 overall dissolution rate of HCTZ was higher in tablets containing lactose compared to DPD tablets (even in the acidic medium), this
281 example demonstrates the complex interactions between formulation components and their potential to alter dissolution behavior in
282 the different gastrointestinal compartments.

283 **5.2 Binders**

284 Binders are typically used in solid dosage form manufacturing to promote adequate mechanical strength of granules or tablets. Wet
285 binders are used in wet granulation to ensure appropriate granule formation with good flow properties while dry binders are
286 incorporated after the granulation step or in direct compression to facilitate compaction and formation of strong tablets. Commonly
287 used binders include: disaccharides, starches, celluloses and synthetic polymers (polyvinylpyrrolidone, polyethylene glycol).

288 **5.2.1 Microcrystalline Cellulose**

289 Cellulose is a polysaccharide composed by β (1→4) linked D-glucose units forming microfibrils in plant cells (Figure 3). These
290 microfibrils bond together to create large crystalline regions with intervened amorphous parts. Microcrystalline cellulose (MCC) is
291 obtained by hydrolytic depolymerisation of cellulose in order to isolate the crystalline regions with, usually, a subsequent spray drying
292 step to obtain dry and porous particles[66]. Cellulose for MCC production is mainly derived from wood. Different grades of MCC
293 with a variety of particle size/particle size distribution, moisture content and bulk density are available in the market.

MCC is mainly used as a binder/filler in tablet manufacturing, with good disintegrant and lubricant properties. It's functionality as a binder relates to its ability to deform when compression force is applied. MCC particles come in closer contact and form multiple hydrogen bonds leading to strong compacts. Potential critical material properties of MCC with respect to its functionality as a binder include: moisture content, particle size, bulk density, specific surface area, degree of polymerization and crystallinity [4].

Molecular Properties

The degree of polymerization may affect tabletability, with highly polymerized MCC molecules leading to powders with small particle size and smooth surface. These attributes impact flowability (finer fibers with increased adhesiveness) but have a positive effect on tablet hardness. Tablets containing MCC with a degree of polymerization of 244 and 299 were twice as strong as those produced with an MCC with a degree of polymerization of 199 [67]. In general, degrees of polymerization favoring the fibrous structure of the polymer, improve tabletability but compromise powder flowability [4]. Impurities in MCC brands can affect drug stability (hydrolysis, drug adsorption onto the polymer) [49].

Structural Properties

Two MCC polymorphs, MCC I and MCC II, differing on the hydrogen bonding between the microfibrils (parallel and anti-parallel orientation of the MCC chain, respectively) have been described. Powder properties of the two polymorphs show great variation and a twofold difference of the swelling value of the two polymorphs is observed (0.2 mL/g for MCC I vs 0.8 mL/g for MCC II) leading to rapid disintegration of MCC II due to the higher water uptake [68]. The degree of crystallinity/amorphicity has a similar

pattern, and the presence of amorphous regions in MCC affects water penetration that could affect tablet dissolution. MCC undergoing an extra grinding step to reduce crystallinity and generate amorphous structures led to an increase in water penetration owned to hydrogen bonding between the amorphous regions and water [69]. MCC crystallinity has an impact on dissolution, as an increase in water penetration is noted with lower MCC crystallinity. A decrease of the dissolution rate of acetaminophen tablet as MCC crystallinity decreased from 65.5% to 37.6% and subsequent increase of the dissolution rate as the degree of MCC crystallinity was further reduced (25.8% to 12.1%) has been reported [70]. These studies suggest that the crystallinity of MCC could be a critical material attribute that should be examined with respect to dissolution.

Particle Properties

Particle properties impact tablet hardness and dissolution. A decrease in particle size of MCC would increase cohesiveness resulting in production of stronger tablets after compression. A 32 μm decrease in MCC particle size (d_{50}) showed a statistically significant increase in disintegration time of tablets containing otanabant (BCS Class IV drug), spray dried lactose and magnesium stearate [51]. Porosity affects disintegration/dissolution, with water penetration in plain MCC tablets of 15% nominal porosity to be achieved in 19 s compared to 148 s needed for 5% porosity tablets [71].

Level

When MCC is incorporated into solid dosage forms as a binder/diluent, it typically comprises the 20-90% w/w of the tablet [66]. High MCC concentrations, may greatly increase tablet hardness leading to problematic disintegration and dissolution. For this

reason when microcrystalline cellulose is used as a binder, inclusion of a disintegrant is recommended to achieve adequate disintegration and dissolution. As a polymer, MCC tends to swell in aqueous solution, with swelling values of 0.2 mL/g and 0.8 mL/g for MCC I and MCC II, respectively [68]. In high MCC concentrations, the increased viscous layer, caused by swelling, will potentially affect drug release.

Biopharmaceutical Properties

Changing the temperature of the dissolution medium affects MCC functionality. Increasing the temperature of the dissolution medium (water; from 20 °C to 37 °C) resulted in faster swelling and water transport in plain MCC tablets, even though, full disintegration did not occurred throughout the duration of the experiment at both temperatures [71]. Information related to other biopharmaceutical properties of MCC have not been reported.

5.2.2 Hypromellose

Hypromellose, also called hydroxylpropyl methylcellulose (HPMC), is a water soluble nonionic cellulosic polymer substituted with methoxy and hydroxypropyl groups (Figure 4). HPMC is manufactured by chemical modification of cotton or wood derived cellulose. It is used as a wet granulation or dry binder and as a rate controlling release polymer in extended release formulations[72] [72]. The effectiveness of HPMC as a release modifier is advantageous in reducing dosage frequency and sustaining drug blood levels. But it can compromise drug dissolution when used as a binder, where controlled release is not necessary expected, as upon contact with aqueous solutions, the polymer hydrates and forms a viscous gel layer which is thickened when more water penetrates. As the

polymer becomes fully hydrated, it tends to relax and dissolve, in a process called erosion [73]. Drug release when HPMC forms this viscous layer consists of three processes: dissolution in the matrix, diffusion through the gel layer and delivery of the drug in the medium as the polymer erodes [74]. Different grades of HPMC are available in the market according to particle size distribution, viscosity and methoxy:hydroxypropoxyl substitution. These characteristics of HPMC along with its particle size affect the functionality of the excipient.

Molecular Properties

The degree of polymerization and substitution are critical aspects for HPMC performance. Molecular weight and chain length have a direct effect on the viscosity of HPMC aqueous solutions. H-bonding between oxygen atoms in ether groups and water molecules leads to extension of the polymer and formation of a coiled shaped structure. Coiled polymers tend to form more H-bonds, entrap water and form entanglements with other coiled molecules resulting in increased resistance to flow. Therefore, polymers with high molecular weight tend to swell faster and form viscous layers. The gel layer thickness increases with increased molecular weight while erosion of the layer is decreased [75]. A counter effect of HPMC molecular weight on gel formation has been reported. Increased molecular weight results in improved swelling properties but reduces water penetration, as the high number of entanglements lead to a less porous layer [76]. Since water penetration affects drug release and dissolution, HPMC molecular weight could be considered as a critical material property whose variation impacts release and dissolution. When three differently substituted HPMC grades were used in acetazolamide (poorly soluble drug) tablet (HPMC 2910, HMPC 2208, HPMC 2906; the first two digits

indicate the % methoxy groups and the two last digits the % of hydroxypropyl group) a decrease in drug release was found with a rank order HPMC 2910> HPMC 2208> HPMC 2906 [77]. Not only the hydroxypropyl content and the degree of substitution but also the substitution pattern affects release and dissolution. Heterogeneity in substitution pattern alters the release of the polymer due to hydrophobic interactions between the substituents [78] with an expected subsequent drug release alteration [79]. Variation in substitution pattern causes batch to batch variability and sourcing from different suppliers should be evaluated [80].

Particle Properties

Particle size affects drug release and dissolution through its impact on tablet hardness and water penetration. HPMC of small particle size form stronger tablets due to increased surface area and interparticle cohesiveness, whereas HPMC of larger particles trigger rapid dissolution, as they do not fully occupy space around particles leaving voids for water penetration [81]. HPMC particle sizes above 113 μm increased dissolution rate of aspirin [82]. Drug release was caused by: disintegration for large particle sizes, diffusion for medium sizes and a combination of diffusion and erosion for smaller particle sizes. These effects were attributed to the proximity of polymer particles and the differences in the porosity of the formed hydrogel [82].

Level

The impact of HPMC properties on dissolution depends on the amount of HPMC in the formulation. When used as a binder, HPMC is added in a level of 2-5% w/w [72]. Direct impact of HPMC concentrations on dissolution has been reported for levels >10 % w/w [83]. The level of the polymer makes solid formulations more prone to particle size variation. The faster dissolution observed

with higher HPMC particle sizes due to their porous arrangement [81], is annihilated in high concentrations as more polymer chains are present leaving no spaces for water penetration [81].

Biopharmaceutical properties

From a biopharmaceutical perspective, ionic strength, composition of dissolution medium and presence of food are likely to affect HPMC performance. The presence of salts in the medium affect the hydration of the polymer. Some salts, cause polymer dehydration dependent on salt's affinity to water of hydration (salting-in/salting-out effect) and subsequent loss of gel uniformity leading to inconsistent drug release [84]. NaCl interacts with water and affects the sol-gel formation (thermo-reversible gelation of aqueous polymeric solutions) of HPMC [85]. In an aqueous HPMC solution, the hydroxyl groups of the polymer interact with water through hydrogen bonding. Upon heating, these bonds are disrupted leaving the hydrophobic parts of the polymer exposed to interact with each other with subsequent formation of a gel. Increasing NaCl concentrations (0-0.8 M), as salting out ion, shifts this thermogelation to lower temperatures [85]. Presence of salts in high concentrations will affect gel layer formation and can lead to burst drug release [86]. Low salt concentrations impede polymer erosion, which is more pronounced in low viscosity grade polymers·[87], leading to decreased drug dissolution. Implications caused by the heterogeneity in the gastrointestinal physiological conditions {gastric (35mM NaCl) and intestinal contents (100 mM NaCl) and fasted and fed state conditions [88]} are expected.

The behavior of cellulosic polymer can be strongly related to physiological temperature. In an intersupplier comparison of HPC batches, differences in dissolution rate of HCTZ tablets were reported and attributed to HPC solubility and its cloud point. The cloud

point, that is the temperature above which a polymer solution becomes turbid, relates to polymer's hydrophilicity with less hydrophilic polymers undergoing this transition in lower temperatures, and a less viscous layer is formed in temperatures above it. Therefore, when the HPC brand with a cloud point closer to 37°C was used, faster dissolution of HCTZ from the tablet formulation was observed [89]. Since HPC and HPMC are included in the same polymeric class possessing comparable functionality and properties, a similar behavior is expected for HPMC.

Meal components, such as sugars and fat, interact with HPMC affecting its biopharmaceutical properties. The same ionic effect on HPMC dehydration pattern, has been found for dietary sugars. Dietary sugars cause dehydration of the polymer according to their structure and lactose is one of the most potent disaccharides in inducing HPMC dehydration even in low concentration (0.5 M) [90]. In low sugar concentrations, the decreased erosion leads to thicker gel layers that delay drug diffusion and release on the medium, whereas in higher concentrations, the suppression of the gel formation leads to rapid drug release [90]. The presence of milk reduced caffeine release from tablets containing HPMC. High fat concentrations, relevant to fat content of the medium, were deposited on these tablets at the early stages of gel formation, and the fat layer was still present at later time points. Possible coalescence between fat droplets and phase separation of these lipidic compositions on the formed gel resulted in reduced drug release [91] [92] Furthermore, hydrodynamics of the dissolution apparatus permitted a better understanding of the effect of milk on the release from these tablets containing HPMC. With the flow through cell apparatus the decrease in dissolution rate is more pronounced due to the absence of erosional forces and occurs in lower fat contents than in the basket apparatus [91]. These findings suggest that the fed state

406 affects the release from formulations containing HPMC. Biorelevant dissolution testing could shed light on the complex effect of
407 physiological conditions on excipient functionality and release/dissolution.

408 Dissolution of low and high viscosity grade HPMC in phosphate buffer pH 6.8 studied with surface dissolution UV-imaging
409 revealed that for both grades the gel layer was formed rapidly within 15 minutes. For the low viscosity polymer, the initial high
410 concentrations decreased as the polymer expanded. Then, the gel layer was stabilized from the dissolution of undissolved particles
411 (that contribute to the increased polymer concentrations in close proximity to the sample). As the polymer expanded, its concentration
412 was decreased due to polymer disentanglement forming the diffusion layer and the polymer was completely dissolved and diffused in
413 the bulk (Figure 5a). HPMC of higher viscosity showed increased concentrations in the gel layer but decreased rate of diffusion and
414 dissolution (Figure 5c). When agitation was applied, a thinner layer with lower HPMC concentrations and slow diffusion rate were
415 observed (Figure 5b). The effect of agitation was more pronounced for the low viscosity HPMC, as it was more sensitive to shear
416 force (Figure 5d) [74].

417 **5.3 Lubricants**

418 Lubricants are used in solid dosage forms manufacture to enhance processability of intermediate blends and tablets. Friction or
419 cohesiveness between particles impose a barrier in powder or tablet flowability affecting content uniformity, compaction, tablet
420 hardness and therefore product performance. Lubricants address flowability issues, by adherence to die or particle surfaces and
421 reduction of friction or cohesiveness leading to adequate flow properties. Lubrication involves the creation of a film between surfaces

or interfaces in order to reduce cohesion between particles or adhesion of particles onto surfaces [93]. The most commonly used lubricants include stearates (magnesium, calcium, sodium), talc, waxes and sodium lauryl sulfate. Magnesium stearate properties and behavior are reviewed as it possesses excellent lubricant properties.

5.3.1 Magnesium Stearate

Magnesium Stearate, a salt containing two equivalents of a fatty acid (usually stearic and palmitic acid) and a charged magnesium, is manufactured by a reaction between fatty acid salts and inorganic salts (Figure 6) [94]. Fatty acids can be bovine or vegetable-derived [95]. Its lubricant effect relates to the adherence of the polar moiety on granules or powders while the lipophilic part is oriented away from the particle's surface [96]. Its ability to form a waxy layer around particles and tablets leads to reduced water penetration and dissolution can be compromised due to its hydrophobicity. Lubrication efficiency and dissolution, are inversely related as over-lubrication decreases dissolution rate.

Molecular Properties

A maximum of 4-5% in magnesium weight fraction and a minimum of 40% in stearic acid weight fraction is described in the USP [97]. Magnesium stearate is a mixture of stearic and palmitic salts. The sum of stearic and palmitic acid should encounter for the 90% of total weight fraction [98], but the exact ratio of the stearic (C-18) and palmitic (C-16) acid, composing the commercial magnesium stearate, is not set in the Pharmacopoeia specifications.

Depending on the manufacturing process and humidity, four different hydrates of magnesium stearate can be formed (anhydrate, monohydrate, dihydrate, trihydrate), leading to different crystal habits with altered functionality [99]. When preparing magnesium stearate with a precipitation method, precipitation in pH 9 leads to the formation of the dihydrate form, while precipitation in pH 7 or 11 leads to a lower hydration state [100].

Structural Properties

The different crystal structures identified for the different magnesium stearate hydrates include the plate-shaped structure for the dihydrate and needle-shaped structure for the monohydrate and trihydrate form [100-102]. This difference in shape is attributed to a change in the angle of inclination of the hydrocarbon chain caused by the addition of the water molecule [100]. The different crystalline forms have an effect on the magnesium stearate functionality as an excipient. The monohydrate form produces tablets with lower variability during tablet manufacturing [99].The dihydrate form acts as better lubricant due to its lamellar shape as it shears readily under applied tangential forces [101, 103, 104] and has a lower tendency to cause over-lubrication [99]. The irregularity of commercial magnesium stearate shape, compared to high purity magnesium stearate and palmitate, relates to reduced lubricant properties [104].

Particle Properties

Surface area (SA) and particle size affect magnesium stearate functionality. Increasing the SA of the lubricant (due to particle size reduction) leads to higher adhesion work and a thin homogeneous layer on particle surface, whereas decreasing SA results in

enrichment of the surface with lubricant particles [96]. Larger particles have less tendency to strongly adhere to particle surfaces leading to less uniform coats. In both cases, (strong or thick layer) water will face difficulties in penetrating this layer. The high coverage of particle surfaces with the lubricant during blending reduces interparticle bonding leading to weakened tablets [105]. Investigation of the optimum particle size/SA of magnesium stearate, without compromising any quality attributes, is needed as the two extreme levels both may have a negative impact on drug release.

Level

Since magnesium stearate is hydrophobic and care should be taken when added in solid dosage forms as it can compromise drug release. The amount and the mixing time of magnesium stearate in the formulation are critical dissolution variables; increased levels and longer mixing time reduces drug dissolution from capsules [94]. A range of 0.25-5.0% w/w magnesium stearate is used in drug product development [94]. Increasing magnesium stearate level (0.25%-1.0%-5.0% w/w) decreased indomethacin dissolution, due to the decreased interfacial area between the dissolution medium (acetate buffer pH 5 with 0.1% w/v sodium lauryl sulphate) and the drug [106]. Mechanofusion, a process used to coat particles with fine materials, has been found beneficial for drug dissolution, as coated particles with magnesium stearate exhibited decreased agglomeration and enhanced dissolution [107]. In the case of mechanofused magnesium stearate-coated indomethacin powder, drug dissolution was enhanced only in the early stages of dissolution, and dissolution reached a plateau (~80% drug dissolved) at later stages) with slightly higher concentrations achieved only for the 0.25 and 1% w/w magnesium stearate [106].

5.4 Superdisintegrants

Disintegration is needed in immediate release dosage forms where quick onset of action is desired. A single or a combination of mechanisms have been proposed for the disintegration of solid formulations. Firstly, swelling of the disintegrant can compensate the adhesion forces of other formulation components, causing the tablet fragmentation. Furthermore, the porous structure of several disintegrants and their ability to adsorb water via capillary action (wicking) is a potential mechanism for their action. Finally, fragmentation of tablets can be caused from elastic deformation of disintegrants under pressure and release of high energy upon exposure to water due to the ability of particles to recover their initial structure [108]. Common disintegrants used in solid formulations include: starches, modified starches. The introduction of low concentrations of superdisintegrants as agents providing disintegration within few minutes is optimistic in terms of drug delivery in enhancing the dissolution rate of solid formulations [109]. The most notable superdisintegrants include crosslinked polymers such as: sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone.

5.4.1 Sodium Starch Glycolate

Starch is a polysaccharide consisted of amylose and amylopectin, and can be extracted and processed for pharmaceutical use by several plants including maize, potato, rice, corn. Starch modification can be performed in order to improve its functionality as disintegrant. SSG is the sodium salt of the carboxymethyl ether of starch (Figure 7). SSG derives from starch (from several sources) after two chemical modification processes: substitution to increase hydrophilicity and cross-linking to reduce solubility and gel

formation upon contact with water [110]. It is used in pharmaceutical manufacturing as a superdisintegrant as it acts through rapid swelling due to the adsorption of large amounts of water leading to fast disintegration [111]. The functional mechanism of SSG was revealed by High-Resolution Real-Time Magnetic Resonance Imaging (MRI) through investigation of the direction to which the tablet expands when disintegration occurs. SSG acts through swelling as an omni-directional expansion was observed with different grades of SSG [112]. Different grades of SSG are available according to particle size distribution, sodium chloride content and pH.

Molecular Properties

The degree of substitution, due to the role of the carboxymethyl group on functionality, has to be defined. In USP, the amount of sodium in SSG is set between 2.8-4.2%, whereas the degree of substitution is not specified [113]. Values for the degree of substitution between 0.23-0.32 have been reported [114]. Hydration and swelling of SSG leading to fast tablet disintegration, relate to degree of substitution. An increase in swelling and water uptake observed as substitution increases from 0.20 to 0.29 and the opposite effects at higher substitution. An optimum degree of substitution value between 0.28-0.29 for faster and higher dissolution of aspirin tablets was reported [115]. A higher degree of substitution can lead to increased drug-excipient interactions as weakly basic drugs can be adsorbed onto the polymer [49] Crosslinking in SSG, achieved through the phosphate group, leads to a high spacing between SSG chains facilitates water penetration and swelling and reduce gel formation [109]. The extended swelling of SSG compared to other swelling disintegrants is attributed to this type of crosslinking (e.g. croscarmellose is crosslinked through esterification which does not allow this high spacing between the polymer chains). An increase of 25%-35% of crosslinking, leads to powders with increased

swelling and water uptake with further increase in crosslinking leading to lower swelling and water uptake. An optimum value at medium levels of crosslinking (33-35%) for dissolution of aspirin tablets has been reported [115].

Particle Properties

Particle size affects disintegrant functionality of SSG, with larger particles being more efficient [110]. An approximate threefold increase in particle size of SSG resulted in a proportional decrease in disintegration time [116].It can be speculated though that in the case of super-disintegrants, it is questionable whether a change in the second disintegration time-scale can have a direct major impact on dissolution. An indirect effect of the particle size on dissolution is more likely to be expected through its effect on solution's viscosity. As the particle size of polymers decreases, a more viscous layer is formed due to increased interaction with water, creating a barrier for drug diffusion and leading to delayed dissolution

Level

Typical amount of SSG used in drug formulation ranges between 2%-8% w/w [117]. Low SSG levels (0.25%, 0.5% and 1% w/w) in paracetamol tablets resulted in long and varied disintegration times (60min, 40min, 2-15 min, respectively), whereas at higher SSG levels (2% and 4% w/w) the disintegration time was consistent within one minute [115]. SSG in higher levels (>8% of tablet weight) causes an increase in disintegration time due to the formation of a viscous layer which hinders water penetration in the formulation, irrespective of the API solubility [111].

Biopharmaceutical Properties

The pH of the medium affects SSG functionality[65]. SSG hydrates as the anionic carboxyl group interacts with water[65]. In low pH, the polymer gains its neutral form and a less extended interaction with water is expected.[65] In simulated gastric media (0.1 N HCl, pH=1) an approximate twofold reduction in the swelling value and the water uptake of SSG was observed compared to the values in intestinal media (phosphate buffer, pH=6.8) (Figure 8). Compacts of SSG with spironolactone, filler and lubricant did not show the this variation in water sorption in the two media, a fact attributed to the crystallinity of the polymer and the reduced water accessibility when particles are consolidated in strong compacts [109].

5.4.2 Croscarmellose sodium

CCS is a cross-linked polymer of carboxy methylcellulose. Wood or cotton-derived cellulose reacts with sodium hydroxide and sodium monochloroacetate to produce the carboxyl methyl cellulose in a degree of substitution of 0.7. The excess of monochloroacetate hydrolyzes to glycolic acid which reacts with the sodium carboxy methyl group of the polymer and catalyzes the esterification of this group with the closest polymer chains leading to the formation of crosslinks (Figure 9)[118]. It is used in tablet or capsule manufacturing as a super disintegrant acting mainly through a combination of swelling and wicking. The swelling mechanism of CCS was confirmed by MRI studies, as tablets containing CCS expanded in an omni-directional way [112]. At initial stages, disintegration depended on tablet density and water penetration was reduced as tablet hardness was increased. At later stages, as the polymer swells, new pores were formed and water uptake was no longer related to tablet density. Stronger solid dosage forms resulted

in better disintegration, as their less porous structure caused a greater swelling force to be exerted on tablets and formation of widen pores that facilitate water penetration [112].

Molecular Properties

As swelling of CCS is attributed to the hydration of the carboxy methyl group, the degree of substitution defines CCS functionality. Degree of substitution refers to the total acidic (acid form) and basic (sodium salt) components of superdisintegrants. The basic substituent (level of salt) correlates CCS disintegration to the pH of the medium, as CCS turns to its acidic form on low pH with a subsequent loss of its swelling ability [119]. Measuring the volume median diameter gave higher values for CCS in water compared to HCl 0.1 N [65], indicating a more efficient swelling of the sodium salt than the free acid due to higher hydrophilicity. Acid/base ratio and total degree of substitution vary along different CCS brands. Brands with higher basic substituents exhibit larger settling volumes and higher maximal water uptake and size increase. Variation in disintegration times can be attributed to differences in composition when all other properties, such as particle size are similar [119]. A higher degree of substitution may induce drug-excipient interactions. Exposure of delavirdine mesylate tablets containing CCS to high humidity (40 °C, 75% RH) for 8 weeks led to a decrease in drug's dissolution probably from the conversion of delavirdine to its free basic form due to an interaction between the carboxyl group of the polymer and methanosulfonic acid [120].

Particle Properties

For croscarmellose, as a swelling polymer, a larger particle size is expected to lead to enhanced swelling and fast disintegration. Brands of higher particle size of different croscarmellose suppliers showed increased settling volumes and water uptake [119]. An optimum particle size has not been reported. Since, croscarmellose forms a viscous layer upon contact with water, it should be expected that the notion that smaller particles sizes will form a more viscous layer due to enhanced interactions with water would be applicable

Level

In tablet formulations, CCS is used at 0.5%-5.0% w/w to promote fast disintegration[118]. As CCS swells upon contact with water, an increase in its fraction results in the formation of a viscous gel layer acting as a barrier for product disintegration. For aspirin, ascorbic acid and ibuprofen tablets, an optimal superdisintegrant concentration of 7% of the tablet weight was reported to give best disintegration values and up to this level, disintegration time increased irrespective of drug solubility[111]. Even if the difference in disintegration time is low, dissolution can be greatly affected as the drug will have to diffuse through the viscous disintegrant layer.

Biopharmaceutical Properties

Since CCS is a sodium salt, the pH of the medium affects its ionization. In acidic medium, CCS turns to its neutral form with decreased hydrating and swelling capacity[65], but to lesser extent than the highly swelling SSG (section 5.4.1.) (Figure 8) [109]. Therefore, the functional profile of CCS in the stomach and small intestine is expected to be different. Investigation of the effect of composition and level in solid formulations of CCS on solid dosage form disintegration and dissolution based on biorelevant

approaches would provide an insight on implications for its *in vivo* functionality. CCS may impact drug's permeability as it binds to Ca^{2+} cations and compromises tight junction integrity; an increased ranitidine permeability in the presence of CCS has been reported [121].

5.4.3 Crospovidone

Crospovidone is a water-insoluble nonionic polymer consisted of cross-linked 1-vinyl-2-pyrrolidone monomers (Figure 10). It is manufactured through a popcorn polymerization technique (proliferous polymerization) of the initial monomer leading to the formation of porous particles [122]. Crospovidone, used in solid dosage form manufacturing as a disintegrant, acts via a different mechanism than the swelling starches. When compaction force is applied, the polymer deforms. Upon contact with water, it adsorbs water via capillary action and regains its normal structure releasing an amount of energy capable to break the tablet. This shape recovery was confirmed with MRI as a uni-directional expansion of tablet was observed [112].Crospovidone is considered an excellent excipient leading to fast disintegration without compromising dissolution due to its inability to form a gel [123]. Several grades of crospovidone are available on market differing in particle size distribution (standard, fine, superfine or micronized powder), bulk density, hydration capacity and peroxide specifications.

Molecular Properties

Crospovidone is not substituted and lacks of ionizable groups. Therefore, molecular properties of crospovidone are unlikely to affect excipient's functionality. Residual peroxides, though, in crospovidone may affect the stability of oxygen sensitive drugs [49].

Particle Properties

Monographs define crospovidone into two broad particle size types: A (coarser than 50 μm) and B (finer than 50μm) [124]. For crospovidone, a wicking agent, particle size relates to particle porosity. As size increases, the intraparticular porosity increases as well leading to larger water uptake and faster disintegration [125]. A more thorough consideration of crospovidone particle size specifications could be beneficial. Two equivalent grades of crospovidone powder (Polyplasdone XL and Kollidon CL) with the same particle size distribution from different suppliers showed differences in particle porosity and water uptake. When dicalcium phosphate dihydrate was incorporated in HCTZ tablets, the grade with the higher porosity (Polyplasdone XL) dissolved 33% of the drug in 15 minutes while its equivalent (Kollidon CL) released only 18% in the same time. When Kollidon CL (low porosity crospovidone grade) was compared to a grade of lower particle size from the first supplier (Polyplasdone XL 10), the latter showed increased liquid uptake and greater HCTZ dissolution than the former [125]. Whether this behavior relates to differences in particle size or variation in production processes, it designates that equivalent grades according to monograph specifications may have different functionality and interchange between them should be avoided.

Level

Common levels of crospovidone used in solid dosage forms to provide fast disintegration are 2%-5% w/w [126]. The disintegration time of tablets containing highly soluble drugs (aspirin and ascorbic acid) and crospovidone decreased until a maximum crospovidone level of 8% of tablet weight. Levels higher than 8% w/w led to increased disintegration time. When ibuprofen, a poorly

soluble drug, was formulated with crospovidone in tablet, disintegration time was at its lowest value (30 s) at 8% of tablet weight with no subsequent increase with increased crospovidone level due to a possible effect of crospovidone concentration on tablet hardness. Crospovidone levels higher than 8% of tablet weight produce weaker tablets that disintegrate faster [111]. The effect of crospovidone on tablet hardness and its relation to disintegration should be further investigated.

Biopharmaceutical Properties

pH is unlikely to affect crospovidone functionality, as it is a nonionic non gelling polymer[65]. The swelling values were found 0.50 mL/g in simulated gastric (0.1 N HCl, pH=1) and intestinal (phosphate buffer, pH=6.8) media (Figure 8) due to the absence of ionization and the low swelling ability of crospovidone [109]. Water uptake of disintegrant powder was different in the two media, with values of 0.32 g/s and 0.52 g/s in the gastric and the intestinal media, respectively, due to a potential uncoiling of the chain in acidic medium [109]. This difference, though, was annihilated in compacts containing spironolactone, diluent-binder, disintegrant and lubricant and water sorption of these formulations was unaffected by the different pH. Disintegration times were higher (500 s and 350 s in 0.1 N HCl pH 1 and phosphate buffer pH 6.8, respectively) for lubricated compacts (with magnesium stearate) when compared to the unlubricated ones (150 s in both media). For lubricated compacts, higher disintegration time was observed in gastric media than in intestinal media because of the combination of uncoiled crospovidone chains and reduced water penetration caused by the hydrophobic lubricant [109].

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6. Conclusions

Excipients constitute a major component of solid dosage forms and their use covers a variety of functions, from dosage manufacturing to dosage performance. Their importance as potential causes for final product variability is recognized and efforts in characterizing their critical material attributes have been made. Despite the rising awareness on excipient variability, few reports are addressing their role in drug product dissolution. Examining dissolution inconsistencies is essential, since *in vitro* dissolution testing constitutes a predictive tool of *in vivo* performance apart from its role in quality control testing. In this review, potential critical material attributes of commonly used excipients have been discussed with respect to product performance. Criticality is related to excipient functionality that can be altered according to product components and physiological conditions. A great effort still needs to be made to delineate the complex effects of physiological factors on product performance. We conclude that, despite the challenges imposed, an investigation of the exact excipient mechanisms in drug release is of paramount importance in order to adequately characterize and optimize excipient properties by incorporating the QbD principles.

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900 **Figure captions**

901 **Figure 1:** A. *In vitro (dissolution test)* and B. *in vivo (gastrointestinal environment)* factors reported to affect or be affected by the
902 presence of excipient in the gastrointestinal lumen.

903 **Figure 2:** % HCTZ release versus time from tablets containing A: Croscarmellose sodium and Lactose in i. water (light grey bars) and
904 ii. 0.1N HCl (dark grey bars) B: Croscarmellose sodium and Dicalcium Phosphate (DP) in i. water (light blue bars) and ii. 0.1N HCl
905 (dark blue bars) (mean ±SD, n=6). [modified from [65]]

906 **Figure 3**: Chemical structure of Microcrystalline Cellulose (ChemDraw Professional 15.0).

907 **Figure 4:** Chemical structure of Hypromellose (ChemDraw Professional 15.0).

908 **Figure 5:** % released vs time and distance from the sample of HPMC 15 cP in stagnant (a.) and 0.5mL/min flow rate (b.) and HPMC
909 50 cP in stagnant (c.) and 0.5mL/min flow rate (d.) in phosphate buffer (pH 6.8) with UV dissolution imaging (SigmaPlot 13.0).
910 [modified from [74]]

911 **Figure 6**: Chemical structure of Magnesium Stearate and Magnesium Palmitate (ChemDraw Professional 15.0)

912 **Figure 7***:* Chemical structure of crosslinked Sodium Starch Glycolate (ChemDraw Professional 15.0).

Figure 8: Swelling values of SSG, CCS and crospovidone after 20 minutes dispersion of 500 mg of each superdisintegrant in 10 mL of 0.1N HCl (pH=1) (i.) and phosphate buffer (pH=6.8) (ii.) at room temperature. [modified from [109]]

Figure 9: Chemical structure of Croscarmellose sodium (ChemDraw Professional 15.0).

Figure 10: Chemical structure of Crospovidone (ChemDraw Professional 15.

Tables

Table 1: Material properties related to excipient variability

		Diluents		**Binders**		**Lubricants**	**Disintegrants**		
		Lactose	DP	MCC	HPMC	Magnesium Stearate	SSG	CCS	Crospovidone
Molecular Properties	Composition				✓	✓	✓	✓	
	Hydration	✓	✓			✓			
Structural Properties	Polymorphism	✓	✓	✓		✓			
Particle Properties	Particle size	✓		✓	✓	✓	✓	✓	✓
	Surface area	✓		✓		✓	✓	✓	✓

	Size distribution	✓			✓		✓	✓	✓
Level		✓	✓	✓	✓	✓	✓	✓	✓

DP: Dicalcium Phosphate, MCC: Microcrystalline Cellulose, HPMC: Hydroxypropyl Methylcellulose (Hypromellose), SSG: Sodium Starch Glycolate, CCS: Croscarmellose Sodium

923 **Figure 1**

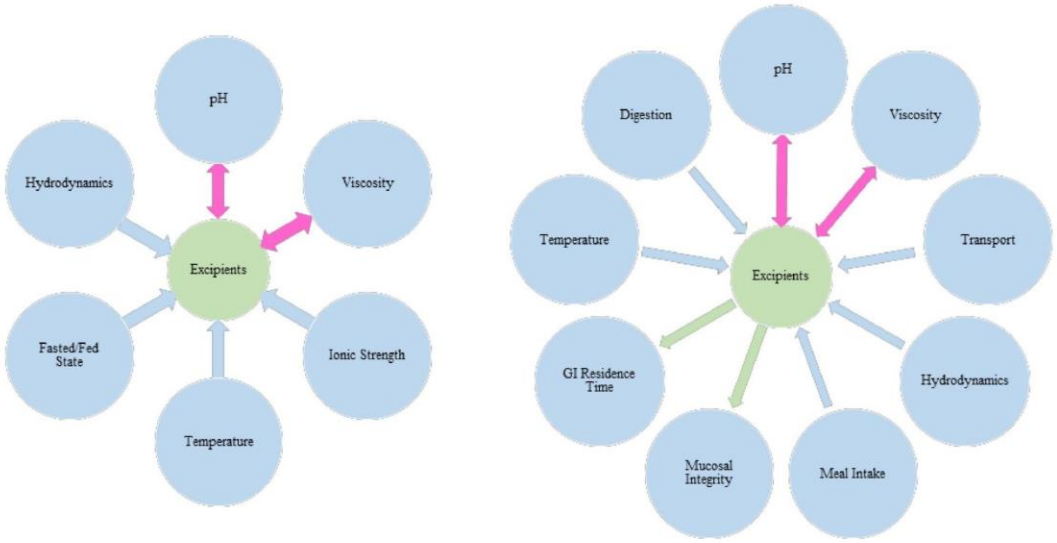

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Figure 2

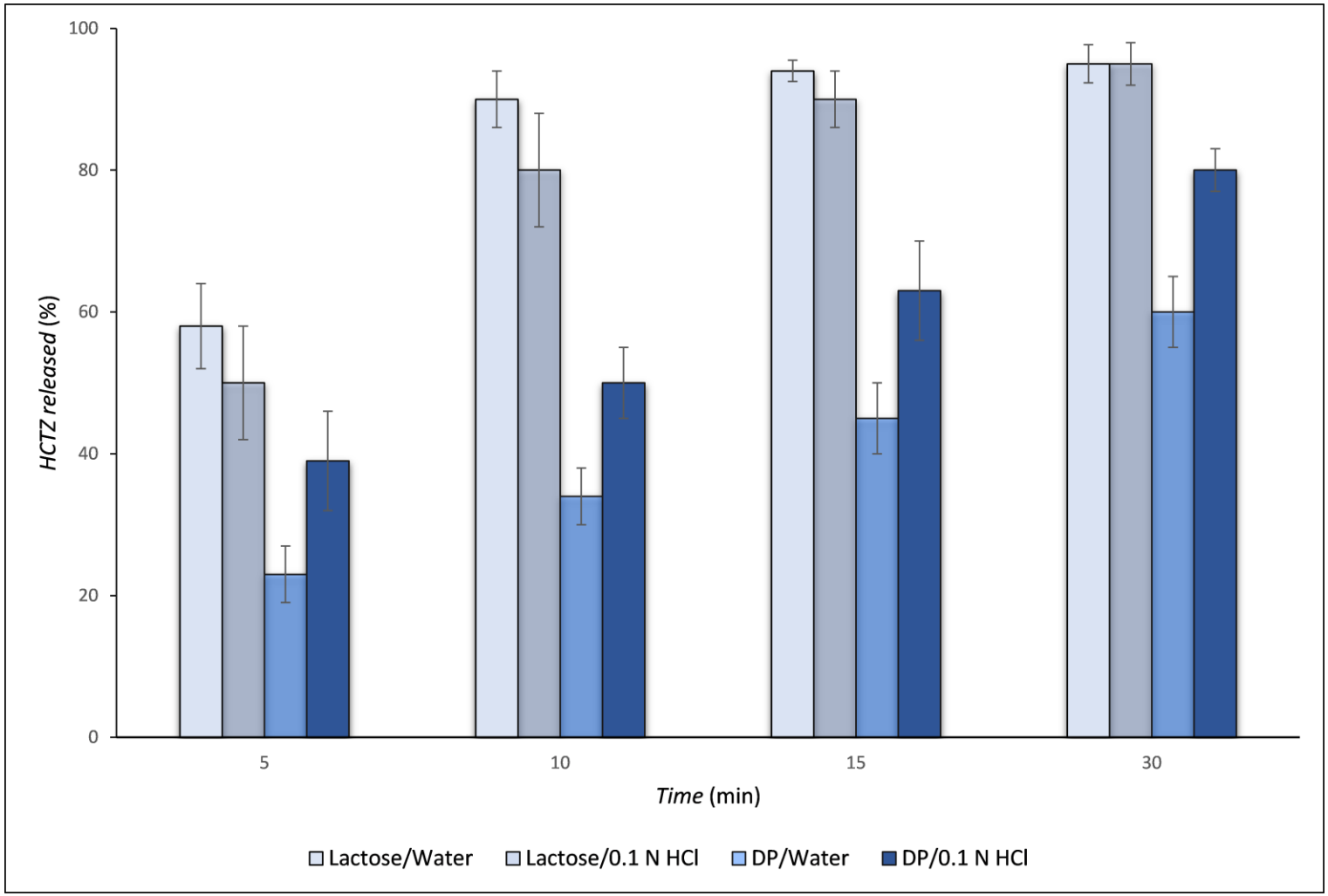
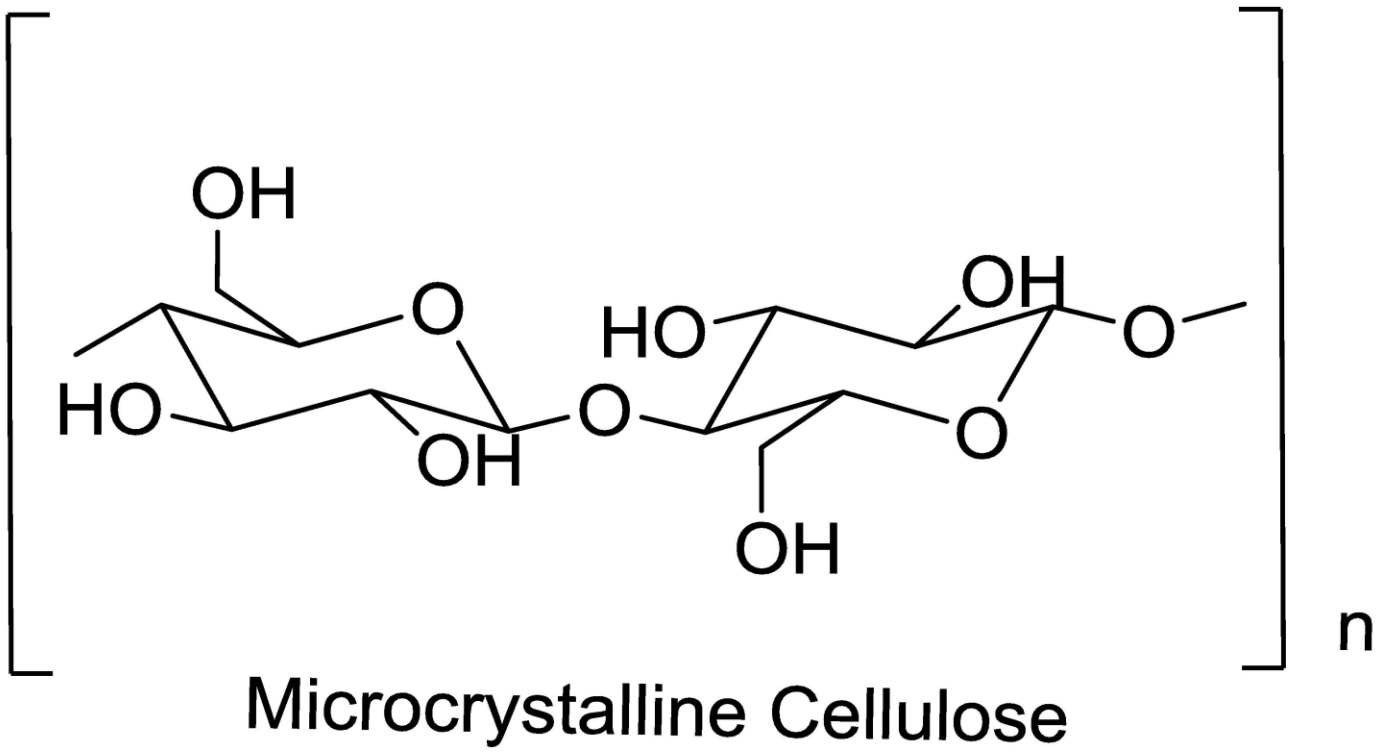
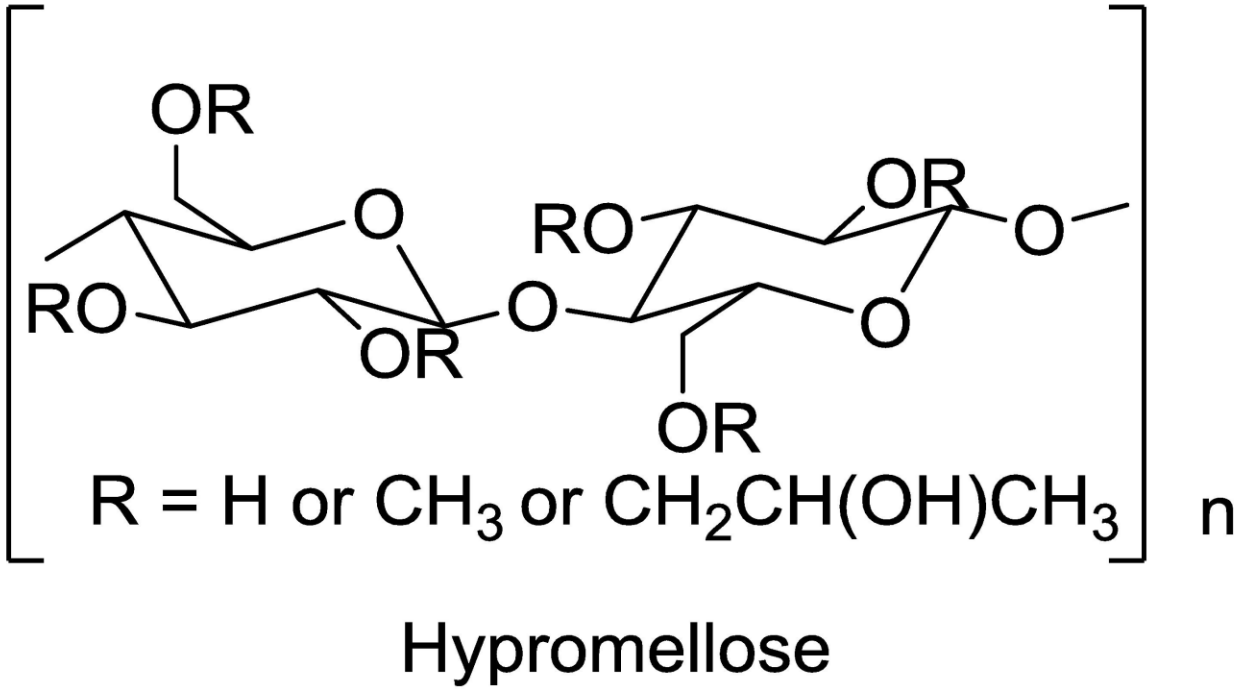

100
80
60
40
20
0
HCTZ released (%)
5
10
15
30
Time (min)
Lactose/Water
Lactose/0.1 N HCl
DP/Water
DP/0.1 N HCl

Figure 3



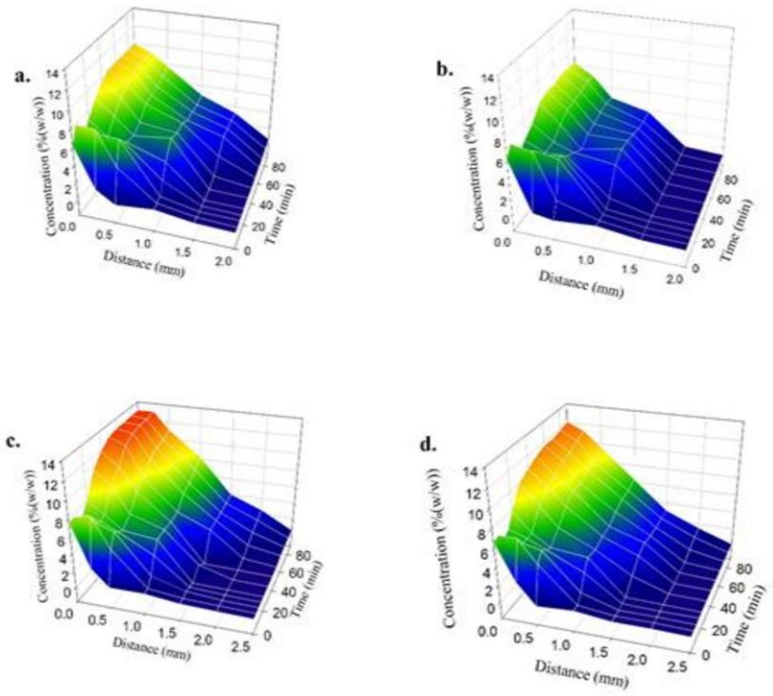
Microcrystalline Cellulose

Figure 4



Hypromellose

935 **Figure 5**



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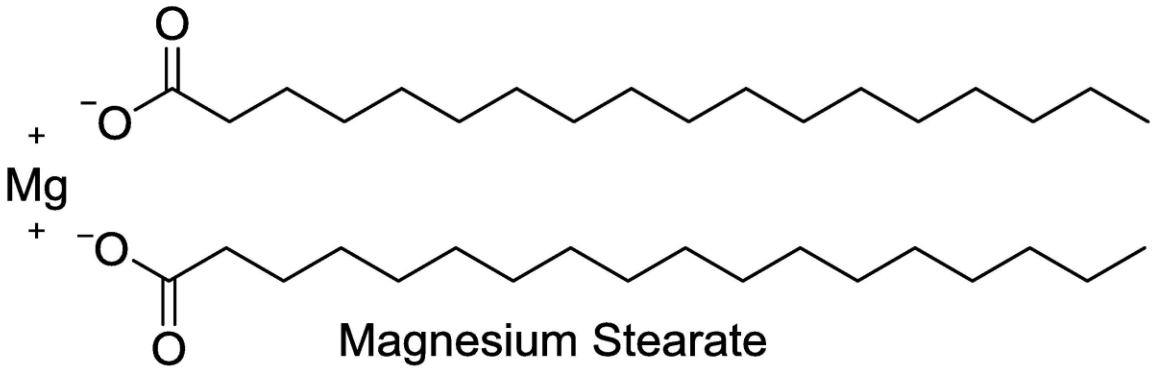
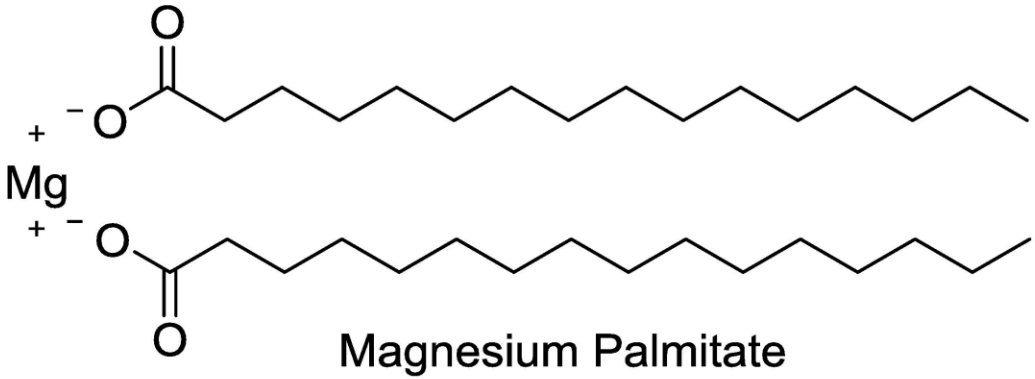
938 **Figure 6**





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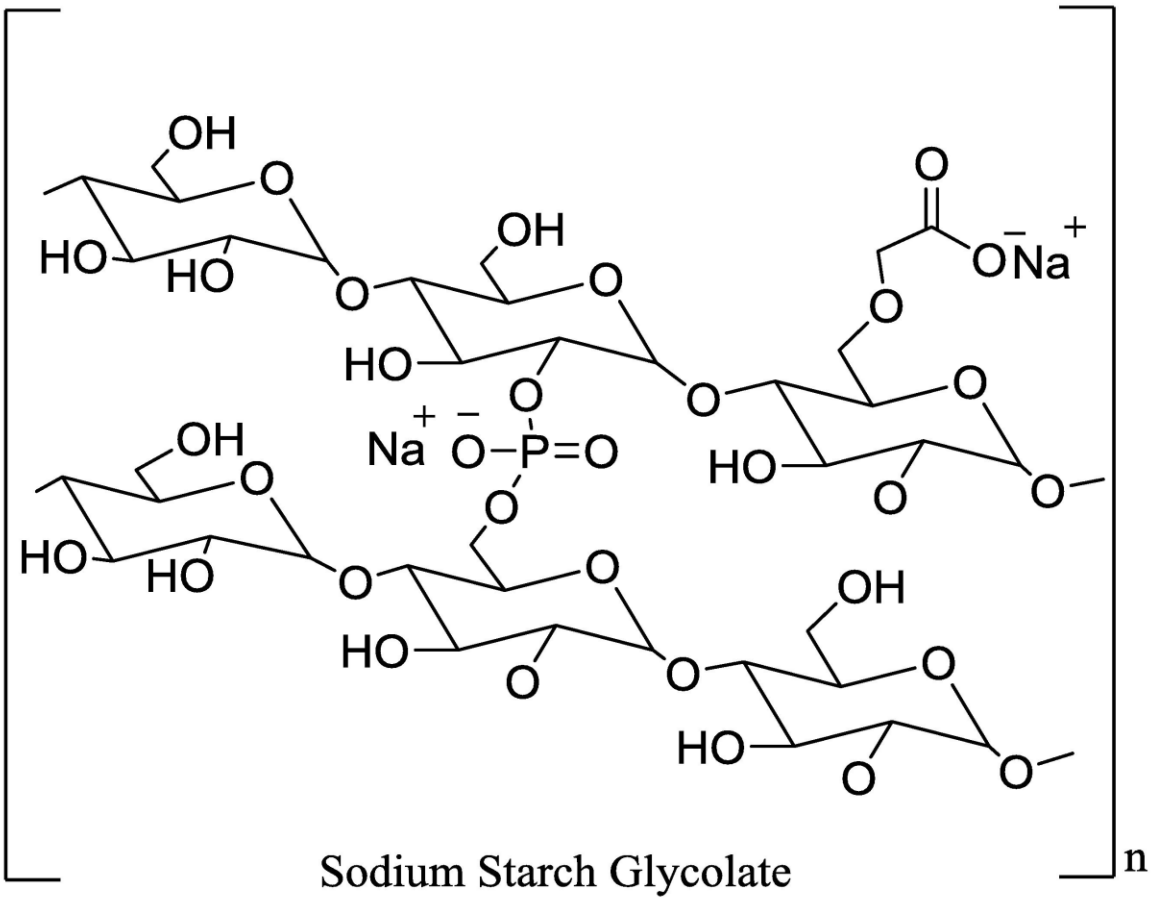
941 **Figure 7**



Sodium Starch Glycolate

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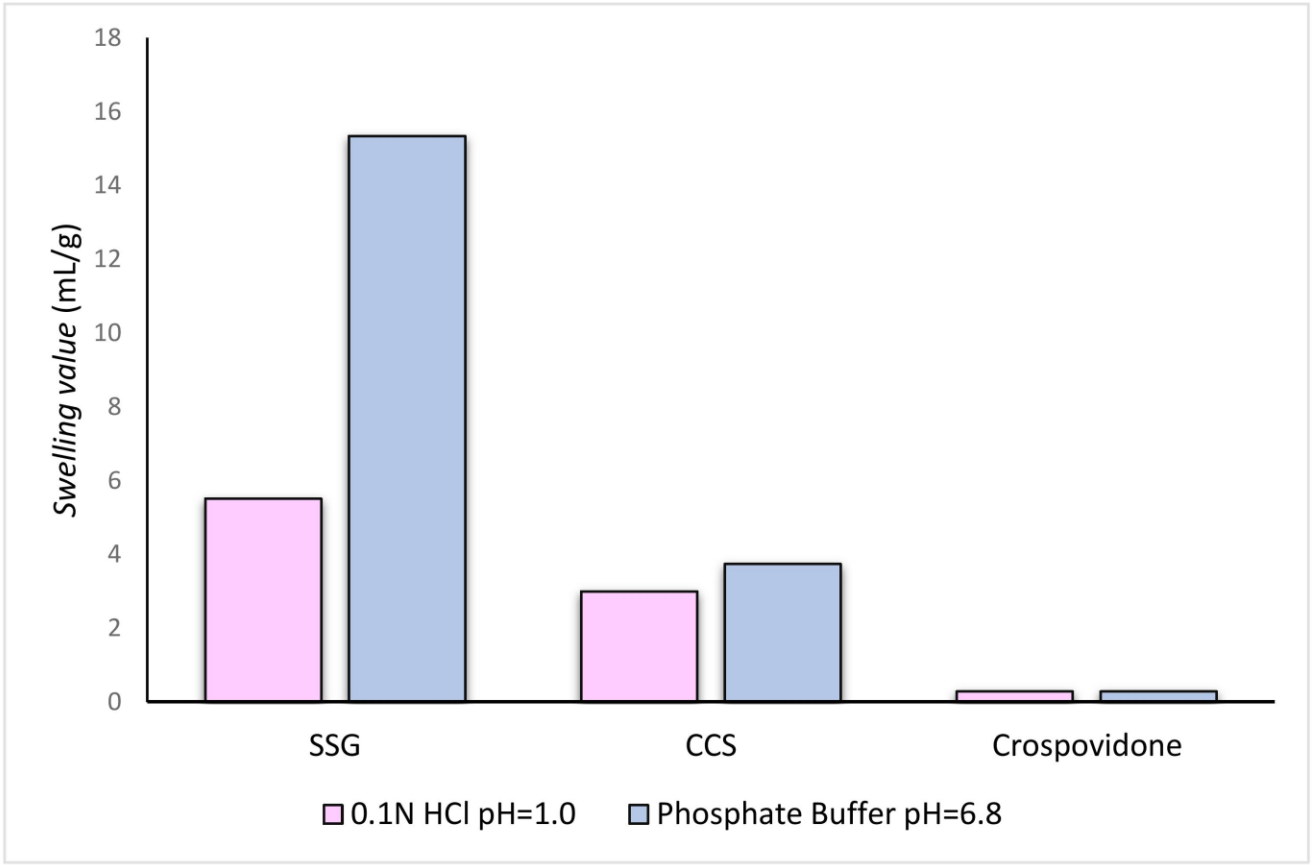
944 **Figure 8**



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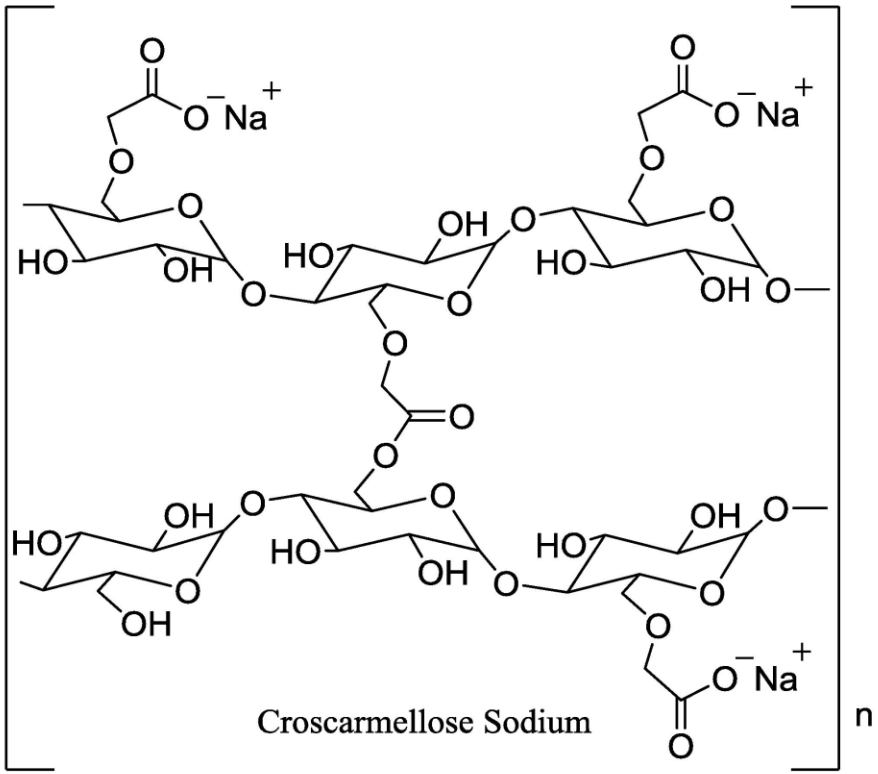
947 **Figure 9**



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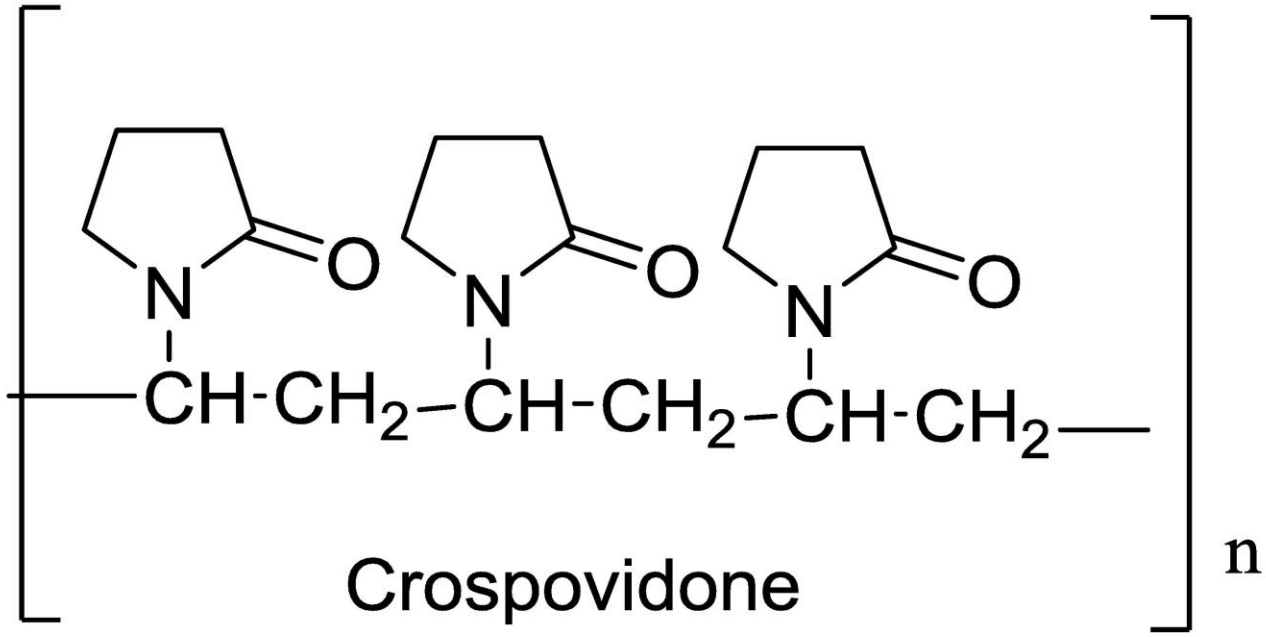
950 **Figure 10**



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